

the amended claims are set forth herebelow, in clean form and as required by 37 C.F.R. § 1.121(c)(1)(i). Pursuant to the requirements of 37 C.F.R. § 1.121(c)(1)(ii), another version of each rewritten claim is submitted herewith at Exhibit Tab A, marked up to show all the changes relative to the previous version of that claim.

Applicants also submit herewith: (1) a Petition for Extension of Time, requesting that the time period for responding to the Office Action be extended for a period of two months (*i.e.*, from APRIL 15, 2002 up to and including JUNE 15, 2002), accompanied by the appropriate fee; and (2) an Amendment Transmittal letter, accompanied by the appropriate fee. It is believed that no additional fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is required or that any refund is owed for this application, please charge the required fee(s) and/or credit the refund(s) owed to our Deposit Account No. 04-0100.

Please amend the application as follows:

**IN THE CLAIMS:**

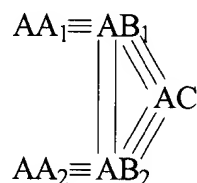
~~Cancel~~ claims 4 and 36 without prejudice or admission.

~~Amend~~ claims 2, 5, 9, 13, 15, 18-19, 23, 27, 34, 37, 41 and 45

without prejudice or admission, as indicated in the attached Exhibit A, so that those claims read as follows:

B/ 2. (Twice Amended) A method of inhibiting osteoclastogenesis

comprising the steps of administering to a patient an amount of an inhibitor effective to inhibit osteoclastogenesis, wherein the inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB<sub>1</sub> is a moiety having a first functional group forming a covalent linkage with one terminus of AC, a second functional group forming a covalent linkage with AB<sub>2</sub> and a third functional group forming a covalent linkage with AA<sub>1</sub> ;

B1  
AB<sub>2</sub> is a moiety having a first functional group forming a covalent linkage with the second terminus of AC, a second functional group forming a covalent linkage with AB<sub>1</sub> and a third functional group forming a covalent linkage with AA<sub>2</sub>;

AA<sub>1</sub> is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB<sub>2</sub>;

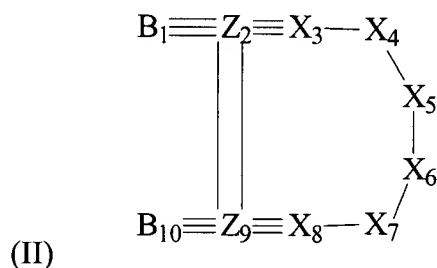
AA<sub>2</sub> is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB<sub>2</sub>;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

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B2  
5. (Amended) The method of Claim 4 wherein the inhibitor has the formula:



wherein:

B<sub>1</sub> and B<sub>10</sub> are each independently a peptide of 1-6 amino acids at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

B2  
Z<sub>2</sub> is a moiety forming a covalent linkage with B<sub>1</sub>, X<sub>3</sub> and Z<sub>9</sub>;

Z<sub>9</sub> is a moiety forming a covalent linkage with B<sub>10</sub>, X<sub>8</sub> and Z<sub>2</sub>;

X<sub>3</sub> is absent or a hydrophilic amino acid;

X<sub>4</sub> is a hydrophobic amino acid;

X<sub>5</sub> is a hydrophobic amino acid;

X<sub>6</sub> is a hydrophobic amino acid;

X<sub>7</sub> is a hydrophobic or hydrophilic amino acid;

X<sub>8</sub> is a hydrophobic or hydrophilic amino acid;

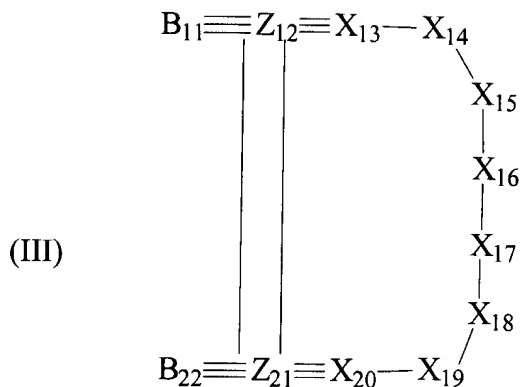
"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

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B3  
9. (Amended) The method of Claim 4, wherein the inhibitor has the formula:



wherein:

$B_{11}$  and  $B_{22}$  are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

$Z_{12}$  is a moiety forming a covalent linkage with  $B_{11}$ ,  $X_{13}$  and  $Z_{21}$ ;

$Z_{21}$  is a moiety forming a covalent linkage with  $B_{22}$ ,  $X_{20}$  and  $Z_{12}$ ;

$X_{13}$  is absent or hydrophobic amino acid;

$X_{14}$  is absent or hydrophilic amino acid;

$X_{15}$  is a hydrophilic or hydrophobic amino acid;

$X_{16}$  is a hydrophilic amino acid;

$X_{17}$  is absent or a hydrophobic amino acid;

B3  
X<sub>18</sub> is a hydrophilic amino acid;

X<sub>19</sub> is a hydrophilic amino acid;

X<sub>20</sub> is a hydrophilic amino acid;

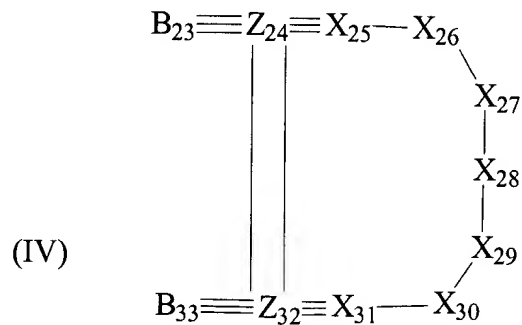
"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

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B4  
13. (Amended) The method of Claim 4, wherein the inhibitor has the formula:



wherein:

B<sub>23</sub> and B<sub>33</sub> are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

B4  
Z<sub>24</sub> is a moiety forming a covalent linkage with B<sub>23</sub>, X<sub>25</sub> and Z<sub>32</sub>;

Z<sub>32</sub> is a moiety forming a covalent linkage with B<sub>33</sub>, X<sub>31</sub> and Z<sub>24</sub>;

X<sub>25</sub> is absent or a hydrophilic amino acid;

X<sub>26</sub> is a hydrophilic amino acid;

X<sub>27</sub> is a hydrophilic amino acid;

X<sub>28</sub> is a hydrophilic amino acid;

X<sub>29</sub> is a hydrophilic amino acid;

X<sub>30</sub> is absent or a hydrophilic amino acid;

X<sub>31</sub> is absent or a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

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B5  
15. (Amended) The method of Claim 14, wherein:

B<sub>23</sub> and B<sub>33</sub> are each independently Tyr or Phe;

Z<sub>24</sub> and Z<sub>32</sub> are each Cys;

X<sub>25</sub> is absent or Arg;

X<sub>26</sub> is Lys;

$X_{27}$  is Glu;

$X_{28}$  is Leu, Pro or Met;

$X_{29}$  is Gly;

$X_{30}$  is absent or Gln;

$X_{31}$  is absent or Val;

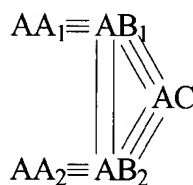
"-" is an amide linkage;

"=" is a disulfide linkage; and

" $\equiv$ " is an amide linkage.

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18. (Twice amended) A method of treating patients who have diseases characterized by bone loss comprising the step of administering to said patient an amount of an inhibitor effective to inhibit such bone loss, wherein said inhibitor is a compound having the formula:



(I)



wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

24 AB<sub>1</sub> is a moiety having a first functional group forming a covalent linkage with one terminus of AC, a second functional group forming a covalent linkage with AB<sub>2</sub> and a third functional group forming a covalent linkage with AA<sub>1</sub>;

AB<sub>2</sub> is a moiety having a first functional group forming a covalent linkage with the second terminus of AC, a second functional group forming a covalent linkage with AB<sub>1</sub> and a third functional group forming a covalent linkage with AA<sub>2</sub>;

AA<sub>1</sub> is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB<sub>1</sub>;

AA<sub>2</sub> is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB<sub>2</sub>;

"=" is a covalent linkage; and

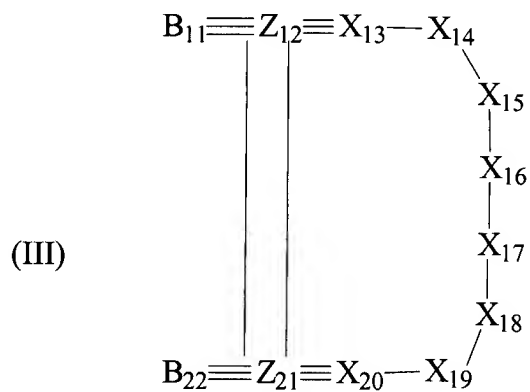
"≡" is a covalent linkage.

19. (Amended) The method of claim 18 wherein the compound has the formula:



"≡" is a covalent linkage.

23. (Amended) The method of claim 18 wherein the compound has the formula:



wherein:

$B_{11}$  and  $B_{22}$  are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

$Z_{12}$  is a moiety forming a covalent linkage with  $B_{11}$ ,  $X_{13}$  and  $Z_{21}$ ;

$Z_{21}$  is a moiety forming a covalent linkage with  $B_{22}$ ,  $X_{20}$  and  $Z_{12}$ ;

$X_{13}$  is absent or hydrophobic amino acid;

$X_{14}$  is absent or a hydrophilic amino acid;

$X_{15}$  is a hydrophilic or hydrophobic amino acid;

$X_{16}$  is a hydrophilic amino acid;

$X_{17}$  is absent or a hydrophobic amino acid;

$X_{18}$  is a hydrophilic amino acid;

$X_{19}$  is a hydrophilic amino acid;

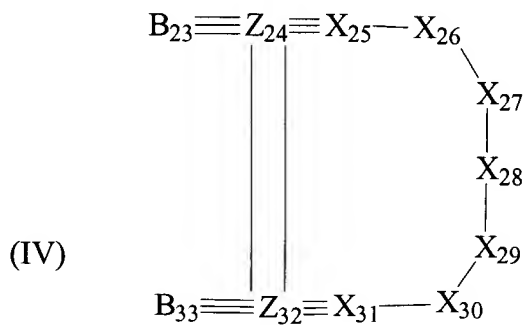
$X_{20}$  is a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

27. (Amended) The method of claim 18 wherein the compound has the formula:



wherein:

B<sub>23</sub> and B<sub>33</sub> are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z<sub>24</sub> is a moiety of forming a covalent linkage with B<sub>23</sub>, X<sub>25</sub> and Z<sub>32</sub>;

Z<sub>32</sub> is a moiety of forming a covalent linkage with B<sub>33</sub>, X<sub>31</sub> and Z<sub>24</sub>;

X<sub>25</sub> is absent or a hydrophilic amino acid;

X<sub>26</sub> is a hydrophilic amino acid;

X<sub>27</sub> is a hydrophilic amino acid;

X<sub>28</sub> is a hydrophobic amino acid;

X<sub>29</sub> is a hydrophobic amino acid;

X<sub>30</sub> is absent or a hydrophobic amino acid;

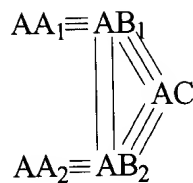
X<sub>31</sub> is absent or a hydrophobic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

34. (Twice amended) A method of inhibiting bone resorption comprising the step of administering to a patient an amount of an inhibitor effective to inhibit bone resorption, wherein said inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB<sub>1</sub> is a moiety having a first functional group forming a covalent linkage with one terminus of AC, a second functional group forming a covalent linkage with AB<sub>2</sub> and a third functional group forming a covalent linkage with AA<sub>1</sub> ;

AB<sub>2</sub> is a moiety having a first functional group forming a covalent linkage with the second terminus of AC, a second functional group forming a covalent linkage with AB<sub>1</sub> and a third functional group forming a covalent linkage with AA<sub>2</sub>;

AA<sub>1</sub> is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB<sub>2</sub>;

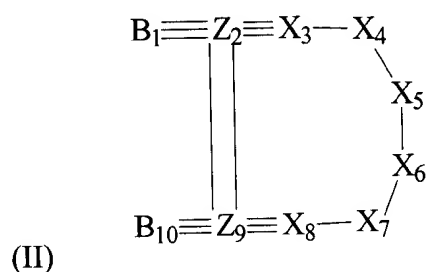
AA<sub>2</sub> is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB<sub>2</sub>;

B9  
"=" is a covalent linkage; and

"≡" is a covalent linkage.

37. (Amended) The method of Claim 36 wherein the inhibitor has the

B10  
formula:



wherein:

B<sub>1</sub> and B<sub>10</sub> are each independently a peptide of 1-6 amino acids at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z<sub>2</sub> is a moiety forming a covalent linkage with B<sub>1</sub>, X<sub>3</sub> and Z<sub>9</sub>;

Z<sub>9</sub> is a moiety forming a covalent linkage with B<sub>10</sub>, X<sub>8</sub> and Z<sub>2</sub>;

$X_3$  is absent or a hydrophilic amino acid;

$X_4$  is a hydrophobic amino acid;

$X_5$  is a hydrophobic amino acid;

$X_6$  is a hydrophobic amino acid;

$X_7$  is a hydrophobic or hydrophilic amino acid;

$X_8$  is a hydrophobic or hydrophilic amino acid;

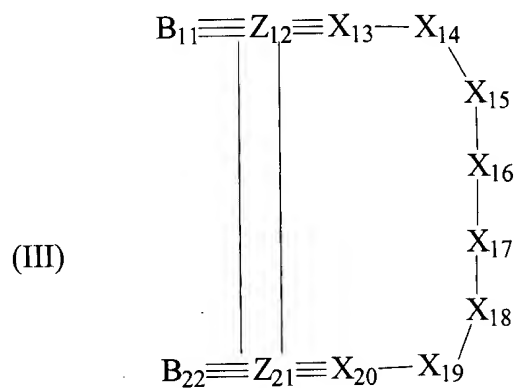
"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

41. (Amended) The method of Claim 36, wherein the inhibitor has the

formula:





wherein:

B<sub>11</sub> and B<sub>22</sub> are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z<sub>12</sub> is a moiety forming a covalent linkage with B<sub>11</sub>, X<sub>13</sub> and Z<sub>21</sub>;

Z<sub>21</sub> is a moiety forming a covalent linkage with B<sub>22</sub>, X<sub>20</sub> and Z<sub>12</sub>;

X<sub>13</sub> is absent or hydrophobic amino acid;

X<sub>4</sub> is absent or hydrophilic amino acid;

X<sub>15</sub> is a hydrophilic or hydrophobic amino acid;

X<sub>16</sub> is a hydrophilic amino acid;

X<sub>17</sub> is absent or a hydrophobic amino acid;

X<sub>18</sub> is a hydrophilic amino acid;

X<sub>19</sub> is a hydrophilic amino acid;

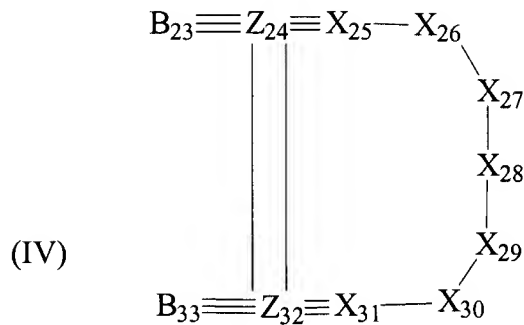
X<sub>20</sub> is a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

45. (Amended) The method of Claim 36, wherein the inhibitor has the formula:



BR2  
wherein:

$B_{23}$  and  $B_{33}$  are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

$Z_{24}$  is a moiety forming a covalent linkage with  $B_{23}$ ,  $X_{25}$  and  $Z_{32}$ ;

$Z_{32}$  is a moiety forming a covalent linkage with  $B_{33}$ ,  $X_{31}$  and  $Z_{24}$ ;

$X_{25}$  is absent or a hydrophilic amino acid;

$X_{26}$  is a hydrophilic amino acid;

$X_{27}$  is a hydrophilic amino acid;

$X_{28}$  is a hydrophilic amino acid;

$X_{29}$  is a hydrophilic amino acid;

$X_{30}$  is absent or a hydrophilic amino acid;

$X_{31}$  is absent or a hydrophilic amino acid;